## REMARKS

Applicants will address each of the Examiner's objections and rejections in the order in which they appear in the Office Action.

### I. Claim rejections under 35 USC §112, second paragraph

In the Office Action, the Examiner rejects Claims 11 and 16-28 under 35 U.S.C. §112, second paragraph, for alleged indefiniteness and under 35 USC §101 for similar reasons. In order to advance the prosecution of this application, Claims 11 and 16-24 have been amended. Applicants respectfully submit that these amendments overcome the Examiner's rejections and request that the rejections be withdrawn.

### II. Claim rejections - 35 USC §112, first paragraph

The Examiner also rejects Claims 1-5, 8-33, 36-40 and 46-50 under 35 U.S.C. 112, first paragraph, for alleged insufficient enablement. While this rejection is respectfully traversed, in order to advance the prosecution of this application, Claims 1, 16 and 22 have been amended. Specifically, these amendments delineate the scope of the independent Claims 1 and 16 to treatment of "cancerous, pre-cancerous, and infectious diseases." Claim 22 has been amended to clarify the intended intracorporeal use.

Applicants believe that the specification provides sufficient scope of enablement to support each of independent Claims 49, 46 and 47 claims. For example, Claim 29 states:

> "Claim 29. A pharmaceutical composition for intracorporeal administration consisting of a halogenated xanthene as the active component for

high energy phototherapeutic treatment using applied ionizing radiation. "

This claim is directed to a pharmaceutical composition (i.e. a drug) that is administered for radiosensitization (i.e., high energy phototherapeutic treatment). The claim does not imply applicability to treating "all other diseased tissue, such as vascular and nasal tissue, ... myocardial infarction, and allergic reaction conditions," as suggested by the Examiner. Instead, the claim is directed to a drug that is administered to tissue for treatment by irradiation of such drug in such tissue. Similarly, Claims 46 and 47 encompass comparable scope:

> "Claim 46. An intracorporeally-applicable radiosensitizer medicament consisting of a halogenated xanthene as the radiodense active component, wherein said medicament is for high energy phototherapeutic treatment, using applied ionizing radiation, of human and animal tissue."

> "Claim 47. A pharmaceutical composition for intracorporeal administration consisting of a dosage unit of a halogenated xanthene suitable for radiosensitization using applied ionizing radiation."

Thus, contrary to the Examiner's position, Claims 29, 46 and 47 do not purport to enable treatment of any disease of any tissue, but rather conform with the teachings of the specification concerning specific types of medicaments (i.e., radiosensitizers) that will be used for radiosensitization.

For at least the above-stated reasons, Applicants respectfully request this rejection be withdrawn.

## III. Claim rejections – 35 USC §102 (Serafini and Neckers)

The Examiner further rejects Claims 1, 3, 5, 8-12, 15-18, 20, 29, 31, 33, 36-39, 46-48 and 50 under 35 U.S.C. 102(b) as being anticipated by Serafini et al., and rejects Claims 1, 3, 5, 8-10, 12, 16, 18, 20, 29, 31, 33, 36-39, 46-48 and 50 under 35 U.S.C. 102(b) as being anticipated by Neckers et al. The Examiner's stated basis for these rejections appears to be that these claims are "drawn to a medicament or pharmaceutical composition *comprising* [a] halogenated xanthene as a primary active component." *(emphasis in original)*

While these rejections are respectfully traversed, in order to advance the prosecution of this application, Claims 1, 3, 5, 11, 16-18, 20, 29, 31, 32, 33, 46 and 47 have been amended. These claims are drawn to radiosensitizer medicaments or pharmaceutical compositions for high energy phototherapeutic treatment "consisting of" a halogenated xanthene as the active radiodense component. Since neither Serafini nor Neckers describe or suggest such medicaments[1], Applicants respectfully submit that each of these rejections have been overcome and request withdrawal thereof.

## IV. Claim rejections – 35 USC §103 (Neckers and Norman)

The Examiner also rejects Claim 14 under 35 U.S.C. 103(a) as being unpatentable over Neckers in view of Norman et al. This rejection is respectfully traversed.

More specifically, in the Office Action, the Examiner combines the teachings of Neckers and Norman to arrive at this rejection. Such a combination is improper for at least the following reasons.

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[1]This is explained in depth in Amendment A, which is incorporated herein by reference.

A. Neckers does not teach any properties of the halogenated xanthenes with respect to ionizing radiation of 1 keV to 1000 MeV.

The Examiner admits that Neckers fails to disclose this feature. Applicants, further, submit that Neckers is not relevant to the claimed invention. More specifically, any discussion of "ionizing radiation" in Neckers is restricted to relatively long wavelength ultraviolet energies. The highest energy (i.e., shortest wavelength) that Applicants have been able to identify in Neckers is a reference to an absorption band at 380 nm (p. 20, last line). Applicants note that 380 nm is equal to 0.003 keV.[2] Typically, molecular spectroscopists such as Neckers never work at wavelengths shorter than approximately 200 nm due to severe technical challenges associated with working at shorter wavelengths, and there is nothing in Neckers to suggest that it diverges from this convention.[3] However, even assuming *arguendo* that Neckers considered or taught much shorter wavelengths, such as for example 10 nm (i.e., 0.124 keV), such energies would still be very different from Claim 14 of the present application.

Accordingly, Neckers has no relevance with respect to the properties of the halogenated xanthenes at energies greater than approximately 1 keV of Claim 14.

B. The gadolinium-based contrast media of Norman are not related to the halogenated xanthenes.

The Examiner states that Norman teaches about certain properties of certain contrast media, such as gadolinium contrast media. The Examiner also contends that these are related to

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[2] Energy (E, in keV) is related to wavelength ($\lambda$, in nm) according to: $E = 1.24/\lambda$.

[3] Applicants note that Neckers provides detailed description of the spectroscopic properties of the halogenated xanthenes at wavelengths between about 400 nm (i.e., 0.003 keV) and about 650 nm (i.e., 0.002 keV).

iodinated chemicals, such as the halogenated xanthenes. However, contrary to the statements of the Examiner, gadolinium and iodine are completely unrelated. According to the periodic table of elements,[4] iodine (symbol "I", element 53) is a member of the Halogens (group YIIB), while gadolinium (symbol "Gd", element 64) is a member of the Lanthanide Rare Earths (group IIIA). According to a standard handbook of chemistry,[5] gadolinium is a ferromagnetic metal with a high magnetic moment; it is presumably these properties that make it useful as a contrast agent for medical resonance imaging (MRI). Iodine, on the other hand, is a halogen that forms compounds with many other elements and, in its pure form, exhibits metalic-like properties. It is not ferromagnetic.

Since gadolinium and iodine are from completely different elemental classes, one skilled in the art reading Norman would not be led to apply knowledge of gadolinium-based contrast agents to the halogenated xanthenes of Neckers. As a result, the required teaching or motivation to combine these references is missing. Hence, the combination of them is improper.

C. Rose Bengal was not known to have usefulness as contrast agent at the time of the invention; thus, Norman would not be led to apply general knowledge of contrast media to the halogenated xanthenes.

The possible use of any halogenated xanthene as a contrast agent for imaging with applied ionizing radiation (i.e., use as a contrast medium) was unknown to the public when the

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[4] See Shleien et al., Handbook of Health Physics and Radiological Health, Third Edition, 1998, p. 2-31. The cited pages are included in the attached Information Disclosure Statement.

[5] See CRC Handbook of Chemistry and Physics, 59th Edition, 1974, pp. B24, B-29 and B-30. The cited pages are included in the attached Information Disclosure Statement.

present invention was filed. United States Patent 6,493,570 was granted to two of the listed inventors of the present invention (i.e., Dees and Scott) for being first to conceive of the novel use of the halogenated xanthenes as contrast agents for methods for imaging with applied ionizing radiation. Prior to these inventors conception, such use is believed to have been unknown to others skilled in the art. This state of the art at the time of submission of the present application is evidenced by the citation for Rose Bengal in a recent edition of the Merck Index, which states that Rose Bengal is known to be useful as a diagnostic agent for corneal abrasion or diagnosis of hepatic function, but does not recite any use as a contrast agent.[6] Accordingly, since possible use of Rose Bengal as contrast media was unknown to Norman (or any practitioner following the teachings in Norman), Norman or any one reading Norman would not be led to apply Norman's paradigm to the halogenated xanthenes.

For at least the above-stated reasons, Applicants respectfully submit that the rejection of Claim 14 under 35 U.S.C. 103(a) over Neckers in view of Norman et al. is improper and request that it be withdrawn.

## V. Claim rejections - 35 USC §102 (Fondren)

The Examiner also now rejects Claims 1, 3- 5, 16, 18, 19, 29, 31-33, 46, 47 and 50 under 35 U.S.C. 102(b) as being anticipated by Fondren et al. This rejection is also respectfully traversed.

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[6] The Merck Index, Twelfth Edition (1996), p. 1422, citation 8421, Rose Bengal. See "Use" and ""Therapeutic Category." The cited pages are included in the attached Information Disclosure Statement.

More specifically, the Examiner's stated basis for this rejection is Fondren's enumeration of six xanthene dyes and their relative toxicities. Applicants submit that this rejection is improper for at least several reasons:

A. Fondren does not disclose a radiosensitizer medicament.

There is no disclosure in Fondren of a radiosensitizer medicament, as recited in the rejected claims. Applicants are not claiming rights to Rose Bengal or any other halogenated xanthene, but rather are claiming certain types of medicaments or pharmaceutical agents for radiosensitization that contain Rose Bengal or another halogenated xanthene as an active ingredient. Accordingly, the agents in Fondren are not the same composition as the claimed invention. For example, Fondren does not describe or suggest medicaments or pharmaceutical agents for intracorporeal use, such as those recited in Claims 1, 16 and 47 of the present application. Nor does Fondren describe or suggest medicaments or pharmaceutical agents for radiosensitization, as recited in independent Claims 1, 16, 22, 29 and 46. Hence, Fondren cannot anticipate nor render obvious such independent claims nor those claims dependent thereupon.

B. Knowledge of toxicity properties does not predict usefulness as a radiosensitizer.

Fondren may disclose certain properties of certain halogenated xanthenes, but such disclosure is not sufficient to disclose the claimed radiosensitizers. Knowledge of toxicity of these xanthenes is an insufficient basis for conceiving that they have the necessary pharmacokinetic properties (i.e., accumulation or retention in cancerous tissue, for instance) and pharmacodynamic properties (i.e., interaction with applied ionizing radiation, thereby serving as

a radiosensitizer) to be an active ingredient in a radiosensitizer medicament.

Therefore, for at least the above-stated reasons, Fondren cannot anticipate nor render obvious the claimed invention. Accordingly, Applicants respectfully request that this rejection be withdrawn.

## VI. Claim rejections under 35 USC §103 (Serafini, Neckers or Fondren)

The Examiner further rejects Claims 2 and 30 under 35 U.S.C. 103(a) as being unpatentable over Serafini or Neckers or Fondren. This rejection is also respectfully traversed.

More specifically, the Examiner's stated basis for this rejection is an opinion that the only substantive difference between the claimed invention and the respective teachings in Serafini, Neckers or Fondren is the "effective variable" of concentration. Applicants dispute this position for at least several reasons:

### A. Serafini does not disclose a radiosensitizer medicament.

The composition in Serafini is a diagnostic agent, not a radiosensitizer medicament.[7] Serafini's diagnostic agent is equivalent to a commercial diagnostic product, Robengatope Sodium Rose Bengal I131 Injection USP, that was sold in the U.S. for approximately 50 years.[8] Under the topic of "Indications and Usage" the package insert notes that the product is "for use as

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[7] Applicants also note that the composition in Serafini *is not a contrast media*, but rather a radiopharmaceutical: the quantity of halogenated xanthene used by Serafini is too small to have use as a contrast media, as characterized by Neckers.

[8] See Squibb (1997), Robengatope, Rose Bengal Sodium I131 Injection USP, package insert J3-381C, rev. Sept. 1977. The cited pages are included in the attached Information Disclosure Statement.

a diagnostic aid in determining liver function and for liver imaging." The product insert does not suggest that it is a therapeutic agent (i.e., as a radiosensitizer medicament) for several reasons: (1) such agents were unknown prior to Applicants' work; and (2) such use would comprise a physically different product (requiring different formulation, specific use instructions and labeling, and separate regulatory licensure with the U.S. Food and Drug Administration). Thus, diagnostic products such as those based on the teachings in Serafini are not the same as the claimed radiosensitizer medicament.

Moreover, as noted supra with respect to Fondren, Applicants' claimed radiosensitizer medicament is not Rose Bengal or any other halogenated xanthene, but rather a distinct medicinal composition (i.e., a therapeutic medicament formulated in sterile, injectible form suitable for intracorporeal administration) that *contains* Rose Bengal or another halogenated xanthene as an active component. Thus, while it would be possible to use, for example, the same starting material (i.e., the reagent Rose Bengal) to produce the compositions in Serafini and those of the present invention, the resulting compositions are distinctly different, as outlined in the table below:

| | Serafini | Present Invention |
|---|---|---|
| Active Ingredient(s) | Radioactive Rose Bengal | Non-radioactive Rose Bengal (or another halogenated xanthene) |
| Indications | Diagnostic aid for determining liver function | Therapeutic for cancer and infectious disease |
| Administration | Sterile intravenous injection | Sterile injection (intravenous, intratumoral, intraperitoneal, ...) |

| | | |
|---|---|---|
| Concentration | 4 mg Rose Bengal / mL (0.4%) | 0.001% to 20% Rose Bengal |
| Regulatory Class | Diagnostic Agent | Therapeutic Agent |
| Practitioners | Radiologists and<br>Internal Medicine Specialists | Oncologists and<br>Interventional Radiologists |

It is clear from this table that the two compositions are not the same.

A fundamental basis for distinction between the chemical compound Rose Bengal and the claimed radiosensitizer medicament is further exemplified by United States Patent 6,707,755 (Somasekhar, et al., "High voltage driver"). This recent patent is for an electronic device based on transistors. While the transistor is notoriously well known and ubiquitous, nonetheless, the claimed device (which contains or is composed of one or more transistors) has been judged to be novel and, rightfully, received protection under Letters Patent. Applicants believe that the instant invention is equally novel in light of the fact that it *contains* Rose Bengal (rather than being Rose Bengal).

Accordingly, the teachings in Serafini are irrelevant to patentability of the claimed concentrations of halogenated xanthene in the present invention.

B. Neckers does not disclose a radiosensitizer medicament.

As discussed supra, Neckers fails to teach or suggest a radiosensitizer medicament that contains Rose Bengal or any other halogenated xanthene. Accordingly, the teachings in Neckers are irrelevant to patentability of the claimed concentrations of halogenated xanthene in the present invention.

C. Fondren does not disclose a radiosensitizer medicament.

As discussed *supra*, Fondren fails to teach or suggest a radiosensitizer medicament that contains Rose Bengal or any other halogenated xanthene. Accordingly, the teachings in Fondren are irrelevant to patentability of the claimed concentrations of halogenated xanthene in the present invention.

In conclusion, the teachings in Serafini, Neckers, or Fondren, taken alone or in any hypothetical combination, fail to disclose or suggest the claimed radiosensitizer medicament containing Rose Bengal or any other halogenated xanthene. Since they fail to disclose the subject of independent Claims 1 ("A radiosensitizer medicament for intracorporeal application ...." ) and 29 ("A pharmaceutical composition for intracorporeal administration ...." ), they can have no relevance to the claimed "effective variables" enumerated in Claims 2 and 30 dependent thereupon. Accordingly, Applicants respectfully request that this rejection be withdrawn.

## VII. Claim rejections under 35 USC §103 (Serafini, Neckers or Fondren in view of Khaw)

The Examiner also rejects Claims 6, 7, 13, 21, 34, 35, 40 and 49 under 35 U.S.C. §103(a) as being unpatentable over Serafini or Neckers or Fondren in view of Khaw. This rejection is also traversed.

More specifically, the Examiner's stated basis for this rejection is an opinion that Serafini or Neckers or Fondren in view of Khaw teach: (A) liposomal targeting of therapeutic agents; and (B) gamma imaging. Applicants dispute both positions for at least several reasons:

A. Liposomal targeting by Khaw is unrelated to the amended claims of the present invention.

Applicants have amended Claims 6 and 34, canceled Claims 7 and 35, and specifically omitted antibodies from these amended claims. These amendments were performed in the spirit of advancing the prosecution of this application and are not believed to be Festo-type amendments. It is believed that these amendments, which remove any superficial similarity to the teachings of Khaw, address the Examiner's basis for rejection of Claims 6 and 34.

B. Khaw teaches use of gamma-emission imaging for diagnostics whereas the instant invention concerns therapeutic use of applied gamma radiation..

The teachings in Khaw are limited to use of gamma radiation in a diagnostic mode. This is made clear by the following passages from Khaw:

> "Labeling and Labels Useful in the Invention
>
> "The various labels listed below need not be limited to labeling of antibodies. Instead of antibodies, other carriers (synthetic or natural) may be used as recipients of the labels.
>
> "(1) Radiolabels
>
> "For imaging purposes, any of the well-known medical radionuclides can be used. Suitable radionuclides include Tc-99 m, I-123, I-125, In-111, In-113 m, Ga-67, or other suitable *gamma-emitters*." (col. 11, lines 33-41, emphasis added)

> "Diagnostic Procedures Using Immunoliposomes
>
> "One diagnostic procedure of the present invention involves diagnosing sites of necrosis in an organ or tissue. This procedure utilizes immunoliposomes specific for intracellular antigens and containing a diagnostic agent, e.g., a detectable molecule such as an imaging agent. One example of such an agent is a *gamma-emitting radionuclide* of the type previously discussed.... The radionuclide-containing immunoliposome is injected (preferably intravenously) into a patient.... Between 30 minutes and 3 days following administration of the labeled antibody, an appropriate scintigraphic imaging technique is employed to image the label that is localized in necrotic tissue. Suitable imaging techniques include *gamma cameras* ...." (col. 16, lines 29- 50, emphasis added)

Thus, Khaw teaches attachment of gamma-emitting radionuclides to diagnostic agents and subsequent imaging of their distribution in the body via detection of gamma emissions from such labeled diagnostic agents. These inherently radioactive diagnostic agents are unrelated to Claims 13, 21, 40 and 49 of the present application, which are directed to therapeutic agents that are activated upon subsequent application of gamma radiation. Not only does Khaw fail to attribute or teach any therapeutic aspect to the agents thereon, but the reference requires (1) inclusion of a radiation emitting element and (2) conjugation of such element to a carrier (such as a immunoliposome or antibody). Neither requirement is encompassed within Claims 13, 21, 40 or 49 of the instant invention. Accordingly, Khaw has no bearing to the present application.

C. Serafini, Neckers and Fondren have no bearing to the claimed invention; and combining these with Khaw fails to yield the claimed invention.

As discussed supra, neither Serafini, nor Neckers, nor Fondren disclose nor suggest the claimed radiosensitizers medicaments that contains Rose Bengal or any other halogenated xanthene. Combination of these teachings with those in Khaw (even if such combination were proper) fails to redress this shortcoming since none of these references suggest a therapeutic agent of any halogenated xanthene upon irradiation with ionizing radiation. Accordingly, alone or in any combination, the references would not have rendered the claimed invention obvious.

Therefore, for at least the aforementioned reasons, Applicants respectfully request that this rejection be withdrawn.

## VIII. Double Patenting

In the Office Action, the Examiner rejects Claims 22-28 under the judicially created doctrine of obviousness-type double patenting over claims of US 6,331,286.

While Applicant respectfully traverses this rejection, in order to advance the prosecution of this application, a terminal disclaimer is being submitted herewith along with a check for $110 for the disclaimer. Accordingly, it is requested that this rejection now be withdrawn.

## IX. Examiner's Response to Prior Arguments

In preparing this Office Action response, Applicants have carefully considered the detailed response of the Examiner to Applicants' prior arguments filed on April 28, 2003. Applicants believe that the claim amendments and supporting arguments contained in the current response address the issues raised by the Examiner. Specifically, Applicants hope that the current claim amendments make it clear that the claimed subject matter is not Rose Bengal or any other halogenated xanthene, but rather specific medicinal agents that contain Rose Bengal. Applicants further submit that such agents are patentably distinct from the cited references, and merit protection under U.S. Letters Patent.

## X. Conclusion

For at least the above-stated reasons, it is respectfully submitted that the claims of the present application are in an allowable form and are patentable over the cited references. Accordingly, it is requested that the application now be allowed.

If any fee should be due for this response, please charge our deposit account 50/1039.

Favorable reconsideration is earnestly solicited.

Respectfully submitted,

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